EXTRA-URETHRITIC CASES IN AN AFRICAN VENEREAL DISEASES HOSPITAL

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It has been said that we treat "*les malades*" and not "*les maladies*". The unit of Medicine is indeed the patient, but the patient is the resultant of many forces and, if we cannot clearly discern these, we fail our patient. In advanced communities, the ranks of many of the more potent causes of ill health have been so thinned that the singled-out raiders are clearly identified as this disease or that. The barriers, moreover, that have been raised against the invaders have grown so extensive that raids may be expected to occur only through certain well defined channels which we have not been able yet completely to block. So it is that in Europe and in the American continent we do perhaps constitute the major diseases our working units, and we form groups of them, such as that of the venereal diseases, according to the particular last channels of approach left open for them to reach us. So good, indeed, in Great Britain is the health of our citizens, thus cared for on the basis of diseases as units, that for what remains to be effected we have had to coin a curious term, "positive health".

Disease in the African patient

Tropical medicine is medicine among primitive communities. We often call the African "a museum of disease" and we never cease to wonder how he tolerates so many major infections and infestations. Medicine in the Tropics is at the stage at which what in advanced communities are major causes of disease appear many together in one patient, setting up their complex interplay of reactions and deleterious processes and precluding our citizen from the attainment of "positive health".

To venereal diseases in the African these remarks are particularly applicable, and it is to illustrate this fact that there follows a survey of 222 patients who, apart from cases of gonorrhoea, were received consecutively from East and West African

TABLE 1—DISTRIBUTION OF KAHN, ITO-REENSTIERNA AND FREI POSITIVITY AMONG EAST AND WEST AFRICANS

	East	West	Total
Number of consecutive non-urethritis admissions	159	63	222
Percentages of men of West and East Coast origin	72	28	—
Number of more or less Kahn positive cases	86	38	124
Number of more or less Reenstierna positive cases	135	52	187
Percentage of Reenstierna positive cases	86	83	84
Number of more or less Frei positive cases	75	32	107
Percentage of Frei positive cases	47	51	48

military units into the venereal disease wards of a base hospital. It should, however, be explained that a dominant motive in the survey was the sorting out of cases of lymphogranuloma inguinale (lymphopathia venereum).

Kahn, Ito-Reenstierna and Frei reactivity among African patients

The 222 patients under discussion came to the clinic as cases of venereal disease other than gonorrhoea. As Table 1 shows, roughly a quarter of them were West Africans, the remainder hailing from East and Central Africa and from Rhodesia. The series was taken long before the great reflux of soldiers from the Ethiopian campaign spoiled the clinic's cross-section of African extra-urethritic venereal disease, as usually encountered, by colouring it with an astonishing flood of florid syphilis.

Rather more than half the number of men had positive Kahn reactions, well over three-quarters had positive Ito-Reenstierna reactions, and about half had positive Frei reactions.

The difference between the proportions of East and West Africans who showed these three sorts of positive reactions is not significant, but it confirms my own more widely gained impression that lymphogranuloma inguinale—and possibly syphilis to a less marked degree—is a commoner disease among West than it is among East Africans, whereas ulcus molle (chancroid) is rather more in evidence

TABLE 2—COINCIDENCE IN INDIVIDUAL PATIENTS OF VARIOUS POSITIVE REACTIONS

Kahn negative cases: 98				Kahn positive cases: 124			
Reenstierna negative 7		Reenstierna positive 91		Reenstierna negative 28		Reenstierna positive 96	
Frei. neg. 6	Frei. pos. 1	Frei neg. 38	Frei pos. 53	Frei neg. 24	Frei pos. 4	Frei neg. 47	Frei pos. 49

among men from East Africa. From a glance at Table 3, however, it will be learned that strongly positive Ito-Reenstierna reactions were found more often among West Africans. Table 4 shows that a strongly positive Frei reaction—as indeed any degree of Frei positivity—was certainly a more usual finding in the West African than in the East African.

The intradermal test of Ito-Reenstierna was done for a time with Dmelcos vaccine in treatment strength. Dmelcos in diagnostic strength had to be abandoned as it gave embarrassingly large reactions. Later, when the French source of this vaccine was cut off, a substance called *Ulcero-vaccino*, which was captured from the Italians in Abyssinia, was used.

For the Frei test, antigens prepared from human bubo pus were used throughout. Some of these were made locally, usually by the Medical Research Institute, Nairobi, from material furnished by the clinic. A certain amount of accredited antigen was obtained from time to time through the kind offices of the Medical

TABLE 3—ANALYSIS OF REENSTIERNA POSITIVE CASES

Reactions	Number	Per cent
Reenstierna positive cases among admissions	187	84
„ „ „ „ East Africans	135	85
„ „ „ „ West Africans	52	83
Strongly Reenstierna positive cases among admissions	80	36
„ „ „ „ „ East Africans	56	35
„ „ „ „ „ West Africans	24	38
„ „ „ „ with positive Kahns	96	77
„ „ „ „ „ negative Kahns	91	93
„ „ „ „ „ positive Freis	102	95
„ „ „ „ „ negative Freis	85	74

Research Institute, Johannesburg. Antigens from two or more sources were used on the same individual, simultaneously or in succession, in 61 out of the present series of 222 cases, sometimes with more or less widely varying results. One of the local antigens, in particular, fell into increasing disrepute. It had been prepared from pus from a patient who subsequently proved to have a highly positive Ito-Reenstierna reaction and it was suspected, as time went on, that it was beginning to act more and more as a Ducrey antigen.

Most of the Kahn, Reenstierna and Frei tests were performed, however, on more than one occasion and many of them three or four times and, although some erroneous deductions were probably made, belief in the general mass of the results is fairly well justified.

All the intradermal tests were read and recorded both as to extent and type on each of the four days succeeding the injection and sometimes for a longer period.

TABLE 4—ANALYSIS OF FREI POSITIVE CASES

Frei reactions	Number	Per cent
Frei positive cases among admissions	107	48
„ „ „ „ East Africans	75	47
„ „ „ „ West Africans	32	51
Strongly Frei positive cases among admissions	17	8
„ „ „ „ „ East Africans	8	5
„ „ „ „ „ West Africans	9	14
„ „ „ „ with positive Kahns	53	43
„ „ „ „ „ negative Kahns	54	55
„ „ „ „ „ positive Reenstierna	102	55
„ „ „ „ „ negative Reenstierna	5	14

The readings which were considered most important were those of the third and fourth days, but much importance was also attached to a steady development of the reaction and to the persistence of a definite nodule (Fischer's "Knötchen"). A reaction over 7 millimetres in superficial diameter, especially if palpably raised, constituted a degree of positivity.

Coincidence in the same patient of Kahn, Ito-Reenstierna and Frei positivity

Kahn sero-positivity and the allergies on which the Ito-Reenstierna and Frei reactions depend have so much persistence that to make deductions from them as to main or contributory causation in immediate disease becomes problematical. Nevertheless, every patient is a compound of disease and reaction, and these tests at least afford indications with regard to some of the variables in reactivity.

Saenz states that Frei allergy sets in only when the skin over the adenitis or adeno-periadenitis becomes involved, that is in the second or third week of disease. He says that it then increases as the disease progresses, except in the presence of florid syphilis. Other observers say that allergy begins in the second week. Connor, Levin and Ecker declare that the reaction is always present on the fortieth day of adenitis and that they have seen a case still allergic 39 years after infection.

According to Riou, a Reenstierna reaction appears before a Frei in Ducrey infection acquired simultaneously with lymphogranuloma inguinale, but in simultaneously acquired syphilis the Frei reaction may be delayed up to 3 months. On the other hand, so Riou declares, when the syphilitic infection occurs after that of lymphogranuloma inguinale, the development of the Frei reaction is undisturbed.

From Table 2 it may be seen that of the 222 East and West African patients who were successively examined, 49 (22 per cent) gave some measure of positivity of Kahn, Ito-Reenstierna and Frei reactions. In 104 more (47 per cent) two sorts of positive reactivity were recorded. Only 24 (11 per cent) had positive Kahns alone, and only 38 (17 per cent) positive Reenstiernas alone, whereas but one man presented a positive Frei reaction unassociated with Kahn or Reenstierna reactivity.

When one recalls the essentials of a satisfactory antigen, as enunciated by Frei in 1932, one despairs of ever finding among African patients a case from which the preparation of antigen may be confidently undertaken. Still further is the clinician embarrassed when the laboratory pleads to be presented with a good collection of pus if it is to be expected in return to provide adequate supplies of diagnostic antigen. The clinician can reply only that the climatic bubo is an agglomeration of enlarged glands glued together by a plastic periadenitis and containing small foci of pus. The solution of the supply of adequate quantities

TABLE 5—ANALYSIS OF 222 ADMISSIONS ACCORDING TO STATE OF LYMPH GLANDS

Condition of lymph glands	Number	Per cent
Cases not showing enlargement of lymph glands	34	15
Cases in which enlargement of glands was not confined to groin	61	27
„ „ „ „ „ „ „ confined to groin	127	57
Cases showing enlarged but movable lymph glands—simple adenitis	91	41
„ „ lymph gland masses, fixed but not to skin—periadenitis	36	16
„ „ „ „ swellings fixed to skin—cutaneo-periadenitis	61	27

of Frei antigen must lie with mouse-brain passage. Findlay has told us that people who are allergic to mouse brain itself are not numerous.

The Kahn reaction in Africans

Throughout Africa the proportion of the adult population giving a positive Wassermann or Kahn reaction probably varies between 20 and 50 per cent.

In South Africa, Rauch and Saayman, in the course of routine Wassermann testing at Germiston Ante-natal Clinic for Africans, have found that 40 per cent of those who attended were sero-positive, yet Campbell, analysing 31,000 Wassermann results coming from the Peninsular Maternity and Groote Schuur Hospitals, has given a figure as low as 14·75 per cent for the positives. Addleston has stated that he found nearly 50 per cent of 35 male and female servants had positive or doubtful Wassermann reactions. Humphries, examining Basutoland and Transvaal Basutos at the Witwatersrand Gold Mines, has found 30 per cent positive. Cluver, as Secretary for Public Health in the Union, has estimated sero-positivity for groups of Africans to be between 30 and 35 per cent.

Coming to East Africa, we can gain little light from the large masses of serological results which emanate directly from government laboratories, other than an impression that there is much sero-positivity in existence. In Zanzibar, however, 12 per cent of the African and 8 per cent of the Arab school children have been found to give a positive Wassermann reaction. A higher figure of 15 per cent is given for a school in the outskirts of the town itself. Zanzibar has carried out a still more illuminating investigation, which is reported to have disclosed that, whereas 11·5 per cent of the school children as a whole are sero-positive, no fewer than 58·6 per cent of the adults in the vicinity of these same schools give a positive Wassermann reaction. The difference of 47·1 between the child and adult percentages is ascribed, in the Annual Medical Report for the year 1936, to syphilis acquired after school age, whereas sero-positivity in childhood is attributed to yaws.

A somewhat similar division of responsibility for serological positivity on the West Coast is suggested by Ramsay, who examined 2,600 children and 2,400 adults by the Sachs-Georgi method. He found that the proportion of positive results decreased from the age of 7 to that of 16, and then gradually rose again till, at the age of 42, 50 per cent of the adults were positive.

Syphilis and yaws.—Throughout tropical Africa the question of the divisibility or indivisibility of treponematosis awaits an answer in detailed terms. To the clinician who has dealt with yaws *en masse* and syphilis *en masse*, there are two different diseases. A traveller who journeys up the Tanganyikan railway line from Tabora to Mwanza on Lake Victoria passes over the Sukumaland prairies, which have not far short of a million Africans in them. At the main centres, to-day, he will find cases of syphilis—or at least localized condylomatosis—but he will be hard pressed to obtain a text-book case of secondary yaws. From Mwanza he may cross the Lake to Bukoba, where he will encounter an amazing amount of gonorrhoea and many phagedenic penile lesions, but he will find the incidence of

TABLE 6—ANALYSIS OF THE 34 CASES WITHOUT ENLARGEMENT OF LYMPH GLANDS

Description	Number	Per cent
Cases showing any degree of Kahn positivity	17	50
„ „ „ „ „ Reenstierna positivity	28	82
„ „ „ „ „ Frei positivity	13	38
Cases in which microfilariae were found in the blood (out of 18 cases examined) ..	0	0
Cases showing + + + + or + + + Kahn reaction	7	21
„ „ + + + + or + + + Reenstierna reaction	12	33
„ „ + + + + or + + + Frei reaction	0	0

Note.—There were three + + Freis in this group, one associated with florid syphilis and a + + Reenstierna, the second also with a + + + + Kahn and a + + + Reenstierna and a recent history of syphilis, and the third with confluent preputial ulcers and a + + Reenstierna.

syphilis open to question. From Bukoba the traveller may journey southwards west of the lake to Biharamulo. Suddenly he meets in hospitals and dispensaries many patients of all ages showing most copious framboesiform eruptions. Inevitably, the observer registers two different pictures associated with two different places. If he has been a resident in Tanganyika since before the great bismuth campaign, he registers these different pictures on a time scale: there was a time when florid yaws was common whereas now it is not. To go into further discussion about these disease entities is to land ourselves in confusion. Kenya statistics show a peak in the yaws figures in the year 1930 followed by a steady decline during the next 10 years, side by side with a gradual extension of syphilis; yet, just over the border, Uganda during the same period declares a steady drop in syphilis and an increase in yaws. There are so many aspects to this matter of treponematosis that the truth cannot be

TABLE 7—ANALYSIS OF 91 CASES OF SIMPLE ADENITIS

Description	Number	Per cent
Cases in which enlargement of glands was not confined to groin	35	38
„ „ „ „ „ „ „ confined to groin	56	62
Cases showing any degree of Kahn positivity	56	62
„ „ „ „ „ Reenstierna positivity	71	72
„ „ „ „ „ Frei positivity	39	43
Cases in which microfilariae were found in the blood (out of 45 cases examined) ..	7	16
Cases showing + + + + or + + + Kahn reaction	34	37
„ „ + + + + or + + + Reenstierna reaction	32	35
„ „ + + + + or + + + Frei reaction	3	3

Note.—There were 3 + + + and 6 + + Freis in this group. Of the former, one was associated with a + + + Kahn, a + + Reenstierna, possibly feigned spondylitis and hard buboes of 10 months' history. This patient said he had had a penile sore 5 months previously. The second was a West African with a + + + + Reenstierna and a somewhat indurated sulcus sore. The third, also a West African, had a ± Kahn, a + + + Reenstierna and a balanoposthitis since childhood. Although he had merely "shotty" lymph glands, his Frei reaction with a South African antigen was + + + +, with a local antigen + + +. Of the 6 + + Frei cases, one was an East African with venereal warts, a + + + + Kahn and a + + + + Reenstierna; the second was a West African with a ± Kahn, a + + + Reenstierna and genital scabs; the third was a West African with condylomata, a + + + + Kahn and a + + + Reenstierna, who exhibited general adenitis and microfilariae in the blood; the fourth, an East African, had a + + + + Kahn, a + + Reenstierna and a soft preputial sore and his Frei was + + + with South African antigen; the fifth case had florid syphilis with + + + + Kahn; the sixth also had florid syphilis with a + + + Kahn, and + + Reenstierna in addition.

shortly stated. On one aspect, however, there has been far too little light shed, namely, the extent to which the African's serological and immunological states have been affected by such treponematosis as has existed among his people. For the moment let us leave the significance and implications of Kahn positivity in Africa at this point; we are in the dark.

The soft sore (chancroid) in Africans

The large part played by the Ducrey's bacillus in African venereal disease is not realized in England. What the Italians aptly term *malattia della miseria* is the common venereal disease in primitive communities having a low standard of hygiene, a term which includes ill-considered and promiscuous sexual intercourse. Franchi, in the Italo-Abyssinian War, found that 87 per cent of cases of phagedenic penile ulcers gave a strongly positive intradermal reaction to Ducrey vaccine. Riou, who was in Senegal, has recorded how the diplobacillus occurs in extragenital ulcers; it has also been observed by myself in extragenital sores in East Africa. Coulter remarks that chancroidal infections are predominant at Alexandria and seem to be regarded very lightly. Coulter proceeds to state that in December 1935 a series of cases appeared, all of which showed signs of severe secondary syphilis. These cases had been under treatment for chancroid from 3 to 4 months earlier, and so it became necessary to recall the two cardinal rules in controlling and investigating a penile sore: (1) no penile sore should be branded as syphilitic until proved to be so beyond all doubt; (2) no penile sore should be regarded as non-syphilitic until the possibility of syphilis has been thoroughly eliminated.

Differential diagnosis.—In endorsing the demand for observance of these rules in Africa, I should, however, like to stress the difficulty in the differential diagnosis. A large proportion of penile sores, especially preputial and frenal ones, seem genuinely to have originated in injury. Many more have the initial appearances of scabies, herpes preputialis, circinate balanitis erosiva or ulcerative balanoposthitis. Nevertheless, especially among the traumatic, scabetic and herpetic types, the Ducrey bacillus frequently appears and evidence of syphilitic infection is often eventually forthcoming. Both Ducrey's bacillus and *Treponema pallidum*

TABLE 8—ANALYSIS OF 36 CASES WITH PERIADENITIS BUT WITHOUT SKIN INVOLVEMENT

Description	Number	Per cent
Cases in which enlargement of glands was not confined to groin	13	36
„ „ „ „ „ „ „ confined to groin	23	64
Cases showing any degree of Kahn positivity	26	72
„ „ „ „ „ Reenstierna positivity	30	83
„ „ „ „ „ Frei positivity	11	31
Cases in which microfilariae were found in the blood (out of 26 cases examined) ..	4	15
Cases showing ++++ or +++ Kahn reaction	16	44
„ „ ++++ or +++ Reenstierna reaction	17	47
„ „ ++++ or +++ Frei reaction	1	3

Note.—The single case of a +++ Frei in this group showed also a ++++ Reenstierna and microfilariae in the blood; this patient had a generalized adenitis and preputial ulcers with mixed organisms in them. Of the four ++ Freis, one had a ++++ Kahn and a +++ Reenstierna and Ducrey's bacillus in a sulcus ulcer, and a generalized adenitis; a second had a ++++ Kahn, a +++ Reenstierna and *Treponema pallidum* in an ulcer on the shaft of the penis and a generalized adenitis; a third had a negative Kahn, a ± Reenstierna, a granulating preputial ulcer and a large bubo; the fourth had a negative Kahn, a +++ Reenstierna, a soft frenal sore and bilateral buboes. The last two cases were fairly certainly climatic buboes.

(*Spirochaeta pallidum*), indeed, are apt to surprise the searcher in all sorts of atypical lesions. This experience is apparently not confined to Africa, as the reporting in the United States of America of a case in 1942 of amoebiasis of the penis illustrates (Hermann and Berman). In the lesion, the character of which was eventually proved beyond doubt, the streptobacillus *Haemophilus ducreyi* was found and a positive Wassermann reaction also developed. Riou and Dang-vu-Giac believe that the Ducrey's bacillus may remain alive but latent in soft chancres which have already healed and reawaken in syphilitic or other lesions. It must

be recalled, too, how often in the African penile condylomatosis is observed to be unaccompanied by obvious lesions elsewhere; indeed, a monorecidive on the penis is fairly common. The indubitable fact is that the typical Hunterian chancre is deceptively rare in communities with a low standard of hygiene; even among a certain type of patients in Glasgow has this been remarked upon, although I am now unable to trace this observation, made by a woman medical practitioner. In further complication of the problem, we have the Ducrey's bacillus, under

TABLE 9—ANALYSIS OF 61 CASES WITH CUTANEO-PERIADENITIS

Description	Number	Per cent
Cases in which enlargement of lymph glands was not confined to groin	13	21
„ „ „ „ „ glands was confined to groin	48	79
Cases showing any degree of Kahn positivity	25	41
„ „ „ „ „ Reenstierna positivity	57	93
„ „ „ „ „ Frei positivity	45	74
Cases in which microfilariae were found in blood (out of 55 cases examined) ..	10	18
Cases showing ++++ or +++ Kahn reaction	11	18
„ „ ++++ or +++ Reenstierna reaction	28	46
„ „ ++++ or +++ Frei reaction	13	21

Note.—In this group the percentage of ++++ and +++ Freis rises suddenly to 21. Two ++++ Freis are included and this is the only group in which ++++ Freis are encountered. Only one++ Freis occurs in the group.

certain circumstances, giving rise to nodular, infiltrative and even indurative conditions, the last especially in sores in the sulcus. In mixed infections it is probable that the characters of ulcus molle for a time predominate but, as the period of incubation of syphilis ends, the characters of a syphiloma tend to appear. Even with my own rule of examining every penile sore, and the groin glands too, on three successive days, I have found myself falling into the error of discharging a patient to his unit, only to have the man return as a secondary syphilitic patient a few months later.

The inguinal bubo in Africans

If, in Africa, the penile sore presents a pretty problem in aetiology, the inguinal bubo is no less intriguing. With so many penile lesions in patients in this continent and so low a standard of hygiene in respect of them, the stress on the immediate lymph glands must be great and varied. The bacillus of Ducrey seems to be the most forward in the attack upon the lymphatic system and causes any or all of the phenomena of lymphangitis: bubonules, perhaps cellulitis, adenitis, periadenitis and frequently intra-adenitic abscess. The infrequency, however, with which the Ducrey organism can be found in the buboes throws some doubt on its exact aetiological role. Typically, the soft sore bubo, like the soft sore itself, is characterized by pain; it rises rapidly in a well delimited swelling covered by a smooth skin; the material of the diseased gland fuses into a purulent mass surrounded by an abscess wall which is attached to underlying tissues and skin. Eventually the abscess bursts and leaves a cavity, the skin edges of which are reddish cyanotic and often necrotic, the inside walls granulating and covered by detritus. A more chronic process may, however, be the feature, with resolution, suppuration and fibrosis all taking a turn and sinuses and fistulae resulting. What governs this altered reaction or disease process is a matter of conjecture. It may be that infection with the virus of lymphogranuloma inguinale (lymphopathia venereum) is the factor; it may be that, despite the auto-inoculability experienced with Ducrey's bacillus, repeated infection leaves a changed host.

Riou and Dang-vu-Giac have reported 3 cases in which the sequence of events has been a Ducrey chancroid which healed, a bubo of lymphogranuloma inguinale type, groin fistulae, healing of these and then, weeks or months after the original ulcus molle, a chancroid in the

groin with *H. ducreyi* in it. Riou has found in Indo-China 65 out of 128 cases of lymphogranuloma inguinale complicated by syphilis, chancroid and gonococcal or coccal infection. He believes that coccal and lymphogranuloma inguinale infections each have the power of reawakening latent infection of the other.

Surveys of Frei allergy in East Africa are wanting, but in West Africa a group of French workers at Brazzaville, in the French Congo, have obtained positive reactions in from 10 to 12 per cent of the number of Africans examined (10·46 per cent in males, 11·94 per cent in females), with 30·9 per cent of garrison men, 24·69 per cent of prisoners and 43·55 per cent of prostitutes. Among the prostitutes the proportions of positive Frei, Reenstierna and Wassermann reactions were in the ratio 24 : 30 : 26.

Advier in Guadeloupe obtained the following results in cases of adenitis :

	Males	*Females*
Frei reactions without other association	20	10
Frei reactions with soft chancre	15	3
„ „ „ hard „	22	3
„ „ „ both soft and hard chancre ...	6	5
Non-venereal sores	46	4

The survey by Finlayson and Purcell in Cape Town covered only Europeans.

Clinical picture.—The part played in Africa by the virus of lymphogranuloma inguinale is still confused. The adenitis which results from this infection is slowly progressive. It usually picks out first the median inguinal glands, which for a time remain movable. Gradually an oval lobulated swelling forms parallel

TABLE 10—ANALYSIS OF 12 CASES FROM TABLE 9 SHOWING A CHANCROIDAL TYPE OF BUBO

Description	Number	Per cent
Cases in which enlargement of glands was not confined to groin	1	8
„ „ „ „ „ „ „ confined to groin	11	92
Cases showing any degree of Kahn positivity	4	35
„ „ „ „ „ Reenstierna positivity	12	100
„ „ „ „ „ Frei positivity	8	67
Cases in which microfilariae were found in blood (out of 11 cases examined) ..	1	9
Cases showing ++++ or +++ Kahn reaction	2	17
„ „ ++++ or +++ Reenstierna reaction	7	58
„ „ ++++ or +++ Frei reaction	3	25

Note.—In this group of 12 cases, which partook of the unilocular abscess character of a chancroidal bubo, there were 3—all East Africans—with a +++ Frei. All of them, however, had +++ or ++++ Reenstiernas, and one of them had in addition a ++++ Kahn and microfilariae of *W. bancrofti* in his blood.

to the groin fold as a result of a matting periadenitic process. Finally the underlying skin is slowly but surely involved ; it becomes dusky and crinkled and at last breaks down in continuity, with pus-containing sinuses that thread through the depths of the mass. A chronic cuirass-like condition follows in many cases—a cutaneo-periadenitis with stress on the significance of " cutaneo".

Differential diagnosis.—That every gradation between the typical buboes resulting from *H. ducreyi* and lymphogranuloma virus infections, respectively, is present in Africa is not surprising, since it is not unusual for several venereal diseases to be acting together or in succession. To the clinician, faced with a case of the climatic bubo type but in conjunction with a penile sore of ulcus molle characters in which *H. ducreyi* can be demonstrated, the assessment of aetiological factors becomes extremely difficult. What, too, is the clinician to say when confronted with a unilocular suppurating bubo, a highly positive Frei reaction, a fairly strong Reenstierna reaction and an indeterminate sore in which he can demonstrate no particular infective agent ? Or again with a bubo of lymphogranuloma inguinale type, a negative Frei reaction, a penile sore, a highly positive Reenstierna reaction, a positive Kahn reaction and many microfilariae of *Wüchereria bancrofti* evident in the patient's night blood ? Is he to say that this is an adeno-periadenitis of mixed filarial, Ducrey and treponematous origin ?

In many parts of Africa by far the chief factor in the production of surgical conditions is filariasis, and its sequelae are to a very great extent located in and around the external genital organs.

Analysis of cases according to condition of lymph glands

The sites and numbers of enlarged superficial lymph glands were noted in the series of 222 cases at present under review. If the glands were freely movable in the surrounding tissues, an adenitis was recorded ; if they were matted together, however, or were attached to the underlying tissues but not to the skin, a periadenitis was recorded ; if the inflammatory process extended to and involved the skin, the case was assigned to a cutaneo-periadenitic group, although in many instances the skin was reached, distended and perhaps burst by an abscess cavity, rather than itself taking part in any general chronic inflammatory process.

Of the 222 patients, 34 (15 per cent) of the number did not show any enlargement of the lymph glands. In 61 (27 per cent) enlarged glands were confined to the groin and in 127 (57 per cent) they were not so confined. (See Table 5.)

Among the cases without any glandular enlargement (Table 6) 17 (50 per cent) had positive Kahn reactions ; among those with enlargement confined to the groin, 66 (52 per cent) were positives ; whereas among those in whom the enlargement was not confined to the groin, the Kahn positive cases amounted to 41, or 67 per cent. That 23 per cent of the number of cases with enlarged glands elsewhere than in the groin should be Kahn negative is not surprising, as allowance has to be made particularly for filarial adenitis—microfilariae were looked for in 144 cases and demonstrated in 16 per cent of them—and for the possible late effects of an early yaws infection that has left no permanent effect on the Kahn reaction.

Among the 188 patients in whom some enlargement of lymph glands was observed, 91 or 41 per cent of the number of admissions, had simple adenitis, 36, or 16 per cent, periadenitis, and 61 more, or 27 per cent, periadenitis involving the skin. From the analyses of these groups in Tables 7, 8 and 9, and from a comparison of these with the analysis of the cases having no enlargement of lymph glands in Table 6, some inferences as to the aetiology of adenitic and periadenitic processes seem worth considering. Kahn positivity, which occurs in 50 per cent of the number of cases without adenitis, rises to 62 per cent among the simple adenitis cases and to 72 per cent among the periadenitis cases, but drops to 41 per cent in the comprehensive cutaneo-periadenitis group. Reenstierna positivity remains fairly constant throughout these groups : 82 per cent among those without enlarged glands, 72 per cent among the simple adenitis cases, 83 per cent among the periadenitis cases, and 95 per cent in the cutaneo-periadenitis group. Frei positivity in the groups was 38 per cent when no glands were enlarged, 45 per cent when a simple adenitis was recorded, 31 per cent when

TABLE 11—ANALYSIS OF 8 CASES SELECTED FROM TABLE 9 AS CLINICALLY GOOD EXAMPLES OF LYMPHOGRANULOMA INGUINALE

Description	Number	Per cent
Cases in which enlargement of glands was not confined to groin	0	0
„ „ „ „ „ „ „ confined to groin	8	100
Cases showing any degree of Kahn positivity	2	25
„ „ „ „ „ Reenstierna positivity	7	88
„ „ „ „ „ Frei positivity	8	100
Cases in which microfilariae were found in blood	1	12
Cases showing ++++ or +++ Kahn reaction	1	12
„ „ ++++ or +++ Reenstierna reaction	2	25
„ „ ++++ or +++ Frei reaction	7	88

Note.—The clinician seemed to be justified by the 100 per cent Frei positivity and still more by the 88 per cent highly positive Freis in this group.

Two of the patients, both West Africans, had ++++ Frei reactions and, moreover, an absence of Kahn positivity. They both had *bubons d'emblée*, although one of them had a ++ and the other a +± or +++ Reenstierna reaction.

Five of the patients had +++ Frei reactions. Three of these, all West Africans, showed no Kahn positivity. They all had more or less long-standing *bubons d'emblée*, one with a negative, the second with a ± and the third with a + Reenstierna reaction, the last-mentioned having suppurating sinuses which extend into the bubo. Of the patients with +++ Frei reactions and positive Kahns, one was a West African with a ++++ Kahn, a + Reenstierna and a *bubon d'emblée* with small multilocular abscess formation ; the other was an East African, with a ± Kahn and ++++ Reenstierna, who exhibited a hard recurrent *bubon d'emblée*.

The only case in the group with merely a ++ Frei was also the only one with a genital lesion—a soft frenal ulcer ; he had a ++ Reenstierna too, but the bubo was a relapse of an earlier one three months previously ; his Kahn reaction was negative.

a periadenitis did not involve the skin, and 74 per cent when a periadenitis did involve the skin.

Infective factors.—These figures rather suggest (1) that syphilis is a factor in the production of adenitis and periadenitis but not of cutaneo-periadenitis, (2) that Ducrey infection may be a factor in much of our periadenitis and especially of periadenitis extending to the skin, although many patients may carry at least no permanent lymphadenitic evidence of this infection, and (3) that lymphogranuloma inguinale is a very probable factor in the cutaneo-periadenitis group, but that if it progresses it almost invariably goes on to skin involvement. Microfilariae—and they were sought for in a fair number of cases in each group—were not found in patients who had no glandular enlargement and were found in 16 per cent of the number of those with a simple adenitis, 15 per cent of those with a periadenitis and 18 per cent with a cutaneo-periadenitis. Most of the microfilariae belonged

TABLE 12—ANALYSIS OF 10 FURTHER CASES FROM TABLE 9, SHOWING ++ OR +++ FREI REACTIONS, BUT NOT COMPLETELY TYPICAL OF LYMPHOGRANULOMA INGUINALE

FREI AND REENSTIERNA REACTIONS	KAHN POSITIVE CASES	KAHN NEGATIVE CASES
Frei more marked than Reenstierna	None	3 cases, all tending to lymphogranuloma inguinale type
Frei and Reenstierna reactions about equal	3 cases (one with microfilariae of *W. bancrofti* in the blood and 1 with *H. ducreyi* in the genital sore), all tending to chancroidal bubo type	3 cases, of which 2 (1 with *H. ducreyi* in sore) were of chancroidal bubo type, and 1 (with microfilariae of *W. bancrofti* in the blood) was of lymphogranuloma inguinale type
Reenstierna reaction more marked than Frei	None	1 case (with microfilariae of *W. bancrofti* in the blood) of chancroidal bubo type

Note.—From the third was made one of the local antigens. Owing to anxiety not to forfeit the opportunity of making use of a good collection of pus from a definitely positive Frei case, an antigen was made from the second case before it was realized that *H. ducreyi* was present in the sore and that the Reenstierna was highly positive. This latter antigen subsequently fell into disrepute.

to *Wüchereria bancrofti*, but those of *Acanthocheilonema perstans* were also common and were often associated with the microfilariae of *W. bancrofti*. It appears that some proportion of African lymph gland affection must be ascribed, therefore, to filarial infestation.

It is, however, perhaps more illuminating to compare the percentages of the highly positive (+++ and ++++) cases in the various groups.

High Kahn positivity is seen in 21 per cent of the number of cases in which not any glands are enlarged, in 37 per cent in simple adenitis, in 44 per cent in periadenitis and in 41 per cent in periadenitis with skin involvement. High Reenstierna positivity occurs in 33 per cent when not any glands are enlarged, in 35 per cent in simple adenitis, in 47 per cent in periadenitis and in 46 per cent in periadenitis involving the skin. The series of percentages for highly positive Frei reactions is particularly striking. A highly positive Frei reaction was not obtained in any case showing no glandular enlargement, and was obtained in only 3 per cent each of cases with simple adenitis and periadenitis, but in the cutaneo-periadenitis group there were 21 per cent of +++ or ++++ Frei reactions.

As the group of 61 cases in which the skin was involved (Table 9), included cases in which the skin was distended by an abscess rather than involved in continuity with the periadenitic process, an attempt was made to separate these latter cases in Table 10, whereas in Table 11 were placed 8 cases in which the periadenitic process gradually involved the skin in its own slow progress.

In the former sub-group, 92 per cent of the number of cases showed confinement of glandular enlargement to the groins. In 35 per cent there was a positive Kahn reaction (17 per cent with +++ or ++++ reactions). All the cases showed a positive Reenstierna reaction (+++ or ++++ in 58 per cent), and in 67 per cent there was a positive Frei reaction (+++ or ++++ in 25 per cent). Microfilariae were found in about 11 per cent.

In the latter sub-group, not any glands other than those of the groin were affected. Kahn positivity was present to the extent of 25 per cent of the number of cases (12 per cent with highly positive Kahns). Reenstierna positivity was present in 88 per cent (25 per cent highly positive). Frei positivity was universal and 88 per cent of the number of cases had +++ or ++++ reactions. Microfilariae were found in one of the 8 cases.

Definite cases of lymphogranuloma inguinale

It is now fairly evident that in the production of a certain type of bubo—a bubo in which gland, surrounding tissues and overlying skin have all begun to contribute to the mass, and in which no marked abscess formation is present—the infection which is indicated by a clearly positive Frei reaction has been the preponderant factor. Setting the 8 cases of Table 11 before us, we exclaim: "Eureka!" "The *bubon d'emblée.*" For in all but one there is not any genital lesion to account for the bubo. They are all tough, chronic, cutaneo-periadenitic buboes with little or no suppuration. Only one is associated with microfilariae of *W. bancrofti* in the blood, and this one is threaded with sinuses that would hardly be accounted for by mere filariasis Only one has definitely suppurated and in it the pus is confined in separate small locules. In one the unhealthy skin has slightly ulcerated. In all but the case with suppuration, the history is prolonged: for instance, 50 days; began two months ago; bubo for 6 weeks and sinuses for 20 days; relapse of bubo in the same place 3 months before; 4 weeks; bubo on and off for 8 months; bubo on and off for years. The sub-group indeed is the most compact one separated from the series, all the cases being of buboes of chronic or recurring progression (except for one case), unaccompanied by any present penile lesion (except in one case) and characterized by a slowly progressive cutaneo-periadeno-adenitis and by a highly positive Frei reaction. Yet, despite an unwonted definiteness in diagnosis, not one of these cases presented the material which the laboratory required in order to make a generous supply of Frei antigen. True, only one patient had a definite Kahn reaction (++++), but this one was the case of fairly free suppuration. Another had a doubtful Kahn and a ++++ Reenstierna reaction. Of the remaining 6 patients, all had slight Reenstierna reactions except one—the case of "a bubo for years".

Case report No. 1.—This last patient was a Hausa from Nigeria, who said he had twice been in hospital that year for buboes. On 27.8.40 he was admitted to No. 1 (T) casualty clearing station as a case of lymphogranuloma inguinale, his Frei reaction with a South African antigen being positive. He was treated at the casualty clearing station, apparently with intravenous Dmelcos vaccine. A month later he reached the clinic with his right medial and lateral inguinal glands matted into a mass involving a scarred and puckered skin, through which some sinuses discharged a little pus which contained staphylococci. His Kahn and Reenstierna reactions were negative and he had not any microfilariae in the blood. With two different local Frei antigens he gave +++ reactions. An examination of his blood gave the following results: haemoglobin 91 per cent; colour index 0·92; erythrocytes 4,920,000; leucocytes 12,400; of these there were polymorphonuclears 43 per cent, lymphocytes 42 per cent, mononuclears 1 per cent, eosinophils 13 per cent, basophils 1 per cent.

As only one of the patients in this sub-group of cases of almost certain lympho-

TABLE 13—ANALYSIS OF 19 FURTHER CASES FROM TABLE 9, WITH MILD OR DOUBTFUL FREI REACTIONS

REENSTIERNA REACTION	KAHN POSITIVE	KAHN NEGATIVE
Negative or small	4 cases tending to lymphogranuloma inguinale type	3 cases tending to lymphogranuloma inguinale and 1 case tending to chancroidal bubo type.
Highly positive	6 cases tending to lymphogranuloma inguinale and 1 case tending to chancroidal bubo type	3 cases tending to lymphogranuloma inguinale type and 1 case tending to chancroidal bubo type

granuloma inguinale belonged to East Africa, it may be well to give rather fuller details of the evidence in regard to this man, too.

Case report, No. 2.—He was a Mnyasa with a history of bubo going back 2 years, and he had, not long before arrival, spent 8 months in hospital in Nyasaland. The bubo, which had gradually been enlarging again, consisted of a matted adeno-periadenitic mass which was attached to pink-scarred skin. During his stay at the clinic his hard bubo receded sufficiently for him to be discharged to his unit. Although this patient presented +++ Frei reactions with two different local antigens, he had also a ± Kahn and a ++++ Reenstierna reaction, and it is admittedly possible that the case may have been one of the chronic variety of Ducrey causation.

In Table 12 are set forth 10 further definitely Frei positive periadenitic cases with skin involvement ; the buboes, however, in these cases, were less definitely of clinical lymphogranuloma inguinale character.

In 5 out of the 10 patients in this sub-group, all of whom gave positive Reenstierna but negative Kahn reactions, the bubo tended to be of the lymphogranuloma inguinale type.

Case report No. 3.—One of these men was an East African, an Acholi of Kitgum. He had had the bubo for a week only, but it was a very large and hard periadeno-adenitic mass, although only slightly attached to the skin. His Reenstierna reaction was definitely positive, but his Kahn was negative and there were no microfilariae in the blood. His Frei reactions were +++ to ++++ on 5 occasions with 3 different antigens, including the South African one. Examination of his blood was recorded thus: haemoglobin 90 per cent ; colour index 0·9 ; erythrocytes 5,010,000 ; leucocytes 6,800 ; of these the proportion was polymorphonuclears 29 per cent, lymphocytes 57 per cent, mononuclears 8 per cent, eosinophils 5 per cent, basophils 1 per cent.

In this man the bubo also receded somewhat, and at no time did the patient exhibit a raised temperature or admit to rheumatic pains or symptoms outside the groin region.

In another of the 5 patients mentioned above, pus was taken for the preparation of one of the local antigens. The patient, a Hausa from Nigeria again, exhibited a definitely fluctuating area in the bubo, but the terminal clinical appearance was that of a cutaneo-periadenitis.

From an East African with a +++ Frei reaction, but with a bubo of more chancroidal type, another collection of pus for an antigen was made, and—such was the anxiety not to lose the pus—this was done before it was realized that the man had a +++ Reenstierna as well as *H. ducreyi* in a penile lesion. It was the antigen from this case which fell into disrepute as time went on.

Into Tables 13 and 14 have been divided the remaining cases from Table 9, according to whether or not a very small Frei reaction or none at all was given. Among the cases showing small Frei reactions the bubo tended in 16 cases out of 19 to be of the lymphogranuloma inguinale type. Among the patients without any Frei reactions 9 out of 12 had buboes in which some of the features which are associated with lymphogranuloma seemed to be in the ascendant.

TABLE 14—ANALYSIS OF 12 CASES FROM TABLE 9, WITH BUBOES OF INDEFINITE TYPE AND WITH NEGATIVE FREI REACTIONS

CLINICAL TYPE	KAHN POSITIVE	KAHN NEGATIVE
Chancroidal bubo features predominate	2 cases	1 case
Lymphogranuloma features predominate	4 cases	5 cases (one with microfilariae of *W. Bancrofti* in the blood)

Incidence of lymphogranuloma inguinale in the series

The analysis of the series of 222 patients may be said to bring to light 8 cases of almost indubitable lymphogranuloma inguinale (7 of them in West Africans), and 4 cutaneo-periadenitic cases the diagnosis of which was fairly certain on the basis of clinical appearance and of Frei reactivity. In addition to these, 2 cases which showed periadenitis without skin involvement were considered to be fairly certainly cases of lymphogranuloma inguinale, and 9 more cases of simple adenitis gave Frei reactions strongly suggestive that lymphogranuloma inguinale was at least a contributory factor in causation. The final impression received is that lymphogranuloma inguinale infection is a definitely contributory factor in nearly 10 per cent of the number of cases of extra-urethritic venereal disease seen among Africans, but that it is more a disease of West than of East Africa.

That the clinician—even with the help of the Kahn reaction, the microscope and allergic tests—can give to most cases of enlarged groin glands a single-term diagnosis is denied, as it is also denied that he can, light-heartedly and early, pronounce any penile lesion to be chancroidal or syphilitic. The individual patient, seen apart, is a severe tax on the diagnostician. Seen in mass he tends to fall into one or other of several more or less well defined groups. From such a

grouping of cases, it becomes clear that the old foundations on which lymphogranuloma inguinale became recognized as a distinct nosological entity remain still the surest criteria for the clinician to-day. Lymphogranuloma inguinale, as met, is a "*bubon d'emblée*"—an indolent, torpid, "strumous", "scrofulous" type, chronically progressive—and its final stages merits the old French description of "*l'adénite subaiguë de l'aine à foyers purulents intraganglionnaires*".

Practical deductions

Medicine is the art of easing the individual patient and public health administration is that of improving the well-being of the mass of the community, but both, like painting, utilize the fruits of science. Analysis provides knowledge, but how to use it in the pursuance of our two arts taxes skill in application.

I am inclined to suggest that my deductions are not yet applicable to public health administration in Africa, where effective mass treatment is not yet in sight, because the African is so numerous and so irresponsible that the continuity which is requisite to efficient treatment is a vain hope. We have to fight not syphilis, nor ulcus molle, nor lymphogranuloma inguinale, but venereal disease, and the only weapon seems to be the gradual raising of the standard of personal hygiene, subject to the proviso that any new factor which threatens invasion demands special measures.

The bearing on the treatment of the individual patient leaves room for adjustment according to the provisions which exist in each locality, but the writer believes that so useless is the attempt to treat the African as a butterfly out-patient, who comes to sip his own nectar as he wills, that the treatment of venereal disease can be usefully undertaken only with the patient under a minimum period of continuous control in hospital. The nature of the treatment has therefore necessarily to be as intense and short as possible. In the presence of multiplicity of causation and of an intolerable onus of exact elucidation, it seems reasonable to resort to simultaneous intense courses of medication which are aimed at any cause or contributory cause of which there may be evidence: multiple injections of mapharside for a week for a case with a positive Kahn reaction, sulphapyridine for the ulcus molle and perhaps tartar emetic for the lymphogranuloma inguinale. It is an interesting speculation whether or not the good effects observed in the treatment of the last-named disease from potassium antimonyl tartrate may be due to some effect on a filarial factor, although antimony seems to be a poor weapon against the microfilarial army. These, however, are merely suggestions.

Summary

(1) Two hundred and twenty-two Africans from West, East and Central Africa and Rhodesia were admitted successively (apart from admissions for gonorrhoea) to a venereal disease clinic.

(2) It is claimed that the large measure of coincidence of Kahn, Reenstierna and Frei positivity which was observed among them is typical for Africa, and that clear diagnosis of any penile sore or inguinal bubo in Africa is impracticable.

(3) By analysis of the series, a small group of almost indubitable cases of lymphogranuloma inguinale is isolated.

REFERENCES

Advier, M. (1937) *Bull. Soc. path. exot.*, **30**, 359.
— (1938) *Marseille méd.*, **1**, 456.
Binkley, G. W., Love, W. R., Schwartz, W. F., Hitch, J. M., Jun., and Margard, Grace A. (1938) *Arch. Derm. Syph., N.Y.*, **38**, 383.
Connor, W. H., Levin, E. A., and Ecker, E. E. (1937) (from *J. infect. Dis.*, **60**, 62) Abst. in *Bull. Hyg., Lond.*, **12**, 6.
Coulter, J. L. S. (1937) *J. R. nav. med. Serv.*, **23**, 302.
Desvernois, M. M. R. (1938) *Rev. Méd. Hyg. trop.*, **30**, 224.
Dulaney, Anna A. (1937) *Amer. J. Syph.*, **21**, 667.
Findlay, G. M. (1932), *Lancet*, **2**, 11.
Finlayson, M. H., and Purcell, F. W. F. (1937) *S. Afr. med. J.*, **11**, 335.
Frei, W. (1932) *Klin. Wchnschr.*, **11**, 512.

Grace, A. W., and Suskind, Florence H. (1936) *Arch. Derm. Syph., N.Y.*, **34**, 65.
Haim, A., and Mathewson, C., Jun. (1937) *J. Amer. med. Ass.*, **108**, 961.
Hermann, H. B., and Berman, L. S. (1942) *J. Amer. med. Ass.*, **120**, 827.
Joyeux, B., and Dang-Hank-Kien (1939) *Rev. méd. française de l'extrême orient*, **17**, 131.
Reider, R. T., and Canizares, O. (1938) *Arch. Derm. Syph., N.Y.*, **38**, 930.
Riou, M. (1937) *Bull. Soc. méd.-chir., Indo-chine*, **15**, 452.
Riou, M., and Dang-vu-Giac (1937) (from *Bull. Soc. méd.-chir., Indo-chine*, **15**, 412) Abst. in *Bull. Hyg., Lond.*, **13**, 1.
Saenz, B. (1935) *Arch. Derm. Syph., N.Y.*, **31**, 348.
Tasaki, K., and Kaminura, T. (1937) (from *J. orient. Med.*, **27**, 117) Abst. in *Bull. Hyg. Lond.*, **13**, 3.
Zanzibar, Government of (1936) *Annual Medical Report.*

THE INTENSIVE THERAPY OF EARLY SYPHILIS*

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Intensive therapy for early syphilis was undertaken in certain medical installations of the United States Army in the European Theatre of Operations in April 1943. Its use was gradually extended, and in September 1943 the Chief Surgeon of the Theatre directed that intensive therapy be administered as the treatment of choice for all patients with early syphilis. To date, over 3,000 patients have received this type of therapy and there has not been any mortality from treatment. The present report is concerned with (1) a summary of the reasons for adopting a short-term method of treatment in military practice, (2) the technique of treatment and morbidity therefrom in a series of 775 cases personally observed by the authors and (3) a summary of "follow-up" studies performed four or more months after completion of treatment in 435 cases.

It is recognized that this report is essentially a progress note in regard to the profound and radical changes which syphilotherapy is undergoing at the present time. With more widespread use of intensive arsenotherapy and, more recently, with the discovery by Mahoney, Arnold and Harris that penicillin has marked spirochaeticidal powers, the great desirability of safe compression of adequate treatment for syphilis into days or weeks, instead of months and years, gives promise of being realized. It has long been apparent to syphilologists that, with prolonged methods of treatment, the benefits of arsphenamine and bismuth therapy were being applied to their full extent in only a small fraction of the patients who ought to receive them for the sake of the public health and of the individual welfare of the patient. Stokes has stated that, in properly operated modern civilian clinics with competent tracing personnel, long-term treatment is satisfactorily carried through in only 25 per cent of early cases, and that in only 50 per cent is ultimately satisfactory although irregular treatment achieved. Cole, Heisel and Stroud have pointed out that such treatment is attained in only a few "top" clinics in the United States and that the performance of the average type of clinic in this regard is even less satisfactory.

Military personnel, although subject to rigid control, often cannot be treated regularly for syphilis under conditions of global warfare. The rapid movement of troops, the difficulties of maintaining a clinical record of treatment which will remain with the patient week in and week out and the varying availability of treatment facilities combine to produce significant and dangerous interruptions in its continuity. Under conditions of active combat, routine treatment of syphilis becomes impossible of accomplishment. The effect of such interruption of treatment is measurable with reasonable exactness on the basis of Padget's study of the long-term (5-10 year) results of treatment for early syphilis in 551 patients. Padget found that cure was attained by 83·4 per cent of the number of patients

*A paper read to the Medical Society for the Study of Venereal Diseases, 29th January, 1944.